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Extracorporeal membrane oxygenation as a bridge to lung transplantation

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Abstract. The occurrence of severe graft failure after lung transplantation which appears refractory to conventional treatment represents a difficult situation with regard to the therapeutic strategies available. Of 17 patients undergoing single lung transplantation at our center, 2 developed early graft failure. In both, temporary artificial cardiopulmonary support by means of extracorporeal membrane oxygenation became necessary as a bridge to retransplantation. Both patients were successfully retransplanted after 8 h and 232 h, respectively, of extracorporeal support. Postoperatively, there was a variety of complications. The first patient completely recovered from temporary severe cerebral dysfunction diagnosed as "locked-in syndrome". She was discharged from hospital on the 93rd postoperative day and remains alive and well 10 months after her operation. The other patient recovered well early after retransplantation. Later, however, airway problems developed, requiring the implantation of endotracheal stents. Cachexia and several episodes of viral pneumonia contributed to the progressive deterioration of her clinical status. She finally died after being hospitalized for 5 months after the original operation. These two cases illustrate the feasibility of using extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. [Eur J Cardio-thorac Surg (1991) 5:94–98]

Key words: Lung transplantation – Extracorporeal membrane oxygenation – Graft failure – Heart-lung transplantation – Pulmonary fibrosis

Lung transplantation has recently been introduced into clinical practice by the Toronto group [1]. According to the registry of the International Society of Heart Transplantation, more than 150 isolated lung transplantations were performed world-wide by the end of 1989 with survival rates approaching those achieved after combined transplantation of both heart and lung [3]. Both single lung and double lung transplantation appear to be a promising therapeutic modality but several distinct problems exist. Long term problems may occur related to healing of the bronchial anastomosis with the potential sequelae of bronchial stenosis or bronchial instability [4].

Early postoperatively, the recipient may be at risk for the development of early graft failure occurring immediately after transplantation or within the 1st postoperative week. This complication precipitates a critical situation for the patient if graft failure advances to a stage refractory to conventional treatment including mechanical ventilation.

We report two cases in whom artificial cardiopulmonary support became necessary for early pulmonary failure after lung transplantation. The clinical course of the patients is summarized and the implications are discussed.

Methods

Case 1

A 46-year-old female underwent right lung transplantation for pulmonary fibrosis. Preoperatively, her vital capacity was 1150 ml and the FEV 1 was 950 ml. The lung from a traumatized donor became available. There were no visible signs of either pulmonary contusion or infection on chest X-ray and intraoperative bronchoscopy. The pulmonary function of the donor was adequate and the right donor lung was accepted for transplantation. At the time of implantation the donor lung was found to have an area of pulmonary contusion in the right lower lobe. Additionally, small emphysemateous bullae were seen in the upper lobe. The ischaemic time of the graft was 265 min. Immunosuppression was induced by the daily administration of antithymocyte globulin (1.5 g/kg) and intravenous cyclosporin A (1 mg/kg). Immediately before extubation on the 2nd postoperative day (POD), her temperature rose above 38 °C and repeated chest X-ray films showed persistent pulmonary infiltrates in the right lower lobe. A bacterial pneumonia was diagnosed and vigorous antibiotic treatment was initiated combined with the prophylactic administration of immunoglobulin. Mechanical ventilation was continued. Despite all measures, the function of the trans-

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planted graft slowly deteriorated over the next 8 days. On POD 11, her situation became critical. At that time she was receiving maximum ventilator therapy with an FiO_2 between 0.8 and 1.0 and high respiratory volumes resulting in high peak inspiratory pressures. Using these ventilator settings, her PaO_2 could only be kept just above 60 torr. At that point it was obvious that no improvement of her status could be achieved by conventional therapeutic measures.

Later that day, a second organ donor was identified. While provisions were made for the patient's reoperation, her pulmonary function showed a final decline with severe hypoxia, hypercarbia and metabolic acidosis. It was determined that she would neither be able to survive the few hours necessary for harvesting the second donor lung nor could she be taken to the operating room under these circumstances. The decision was made to use an extracorporeal membrane oxygenation (ECMO) system. Percutaneous vascular access via the groin was used for rapid institution. Since it was anticipated that she would require continuation of ECMO support throughout the reoperation, a veno-arterial perfusion route was chosen. The ECMO circuit consisted of a Scimed Ultrox membrane oxygenator[1], off-line venous reservoir, arterial blood filter and standard cardiopulmonary bypass tubing. The circuit was driven by a centrifugal pump[2]. Instantaneously, bypass flows between 2.5 and 3.5 l/min were achieved. With the ECMO system in place the patient demonstrated with rapid stabilization of blood pressure and oxygenation. Four hours later she was taken to the operating theatre supported by the ECMO system. At reoperation, it became evident that extracorporeal blood flow would not be sufficient to allow for complete oxygenation of the arterial blood once the right pulmonary artery was clamped. A second venous cannula was inserted into the right atrium providing extracorporeal blood flows in excess of 4.5 l/min. Retransplantation of the right lung was successfully performed. Since the second lung graft showed excellent function it was possible to wean the patient from ECMO in the operating room.

Postoperatively, her lung function continued to remain stable. Immunosuppression consisted of OKT3 (0.1 mg/kg per day) for 2 consecutive days and intravenous cyclosporin A was continued. During the 1st postoperative month, continuous mechanical ventilation was required due to severe cerebral dysfunction including deep coma, no reaction to pain and tetraplegia. Her neurology was compatible with a "locked-in" syndrome. She recovered completely from this complication. On POD 20, she developed thrombosis of both the left subclavian vein and left internal jugular vein which was treated by continuous heparin infusion.

On POD 31, interstitial pulmonary infiltrates again were noted on chest X-ray. Cytomegalovirus (CMV) infection was confirmed by CMV early antigen testing. Treatment was initiated with 9(1,3-dihydroxy-2-proproxymethyl)-guanine (DHPG) for 14 days at a dosage of 10 mg/kg per day. Additionally, CMV polyglobulin was administered. On the 44th postoperative day, spontaneous breathing could be started and her further recovery was uneventful until she was discharged from hospital on POD 93. She remains well now, 12 months after her operation, having resumed professional activities as a school teacher.

Case 2

A 32-year-old female with pulmonary fibrosis was referred to our hospital for evaluation as a potential candidate for lung transplantation. In 1968, resection of the left upper lobe had been performed for tuberculosis. She presented with a vital capacity of 650 ml with an FEV1 of 450 ml. Her PaO_2 on room air was 55 torr. She required continuous oxygen supply, temporary support on a home ventilator, had been immobilized for almost 18 months and was severely cachectic at the time of operation.

An organ from a donor who had a severe cerebral injury as a result of a traffic accident became vavailable. Prior to harvesting, the donor had adequate pulmonary function with a PaO_2 of 280 torr at an FIO_2 of 0.6. There were no visible signs of contusion of the donor lung on chest X-ray. Intraoperative bronchoscopy of the donor revealed no endobronchial effusion suspicious of pulmonary infection. The donor lung was accepted for transplantation. The patient underwent right lung transplantation. Cardiopulmonary bypass was used to support her cardiopulmonary function during the implantation procedure. Cannulation for cardiopulmonary bypass was achieved with a right atrial cannula for drainage of the venous blood and a cannula in the right femoral artery for the arterial return. Ischaemic time for this lung graft was 337 min. On reperfusion of the transplanted lung it was noted that atelectatic areas remained within the lower lobe, but weaning from extracorporeal circulation was uneventful. During preparation of the omentum to be wrapped around the bronchial anastomosis, sudden cardiopulmonary decompensation developed. Extracorporeal circulation was reinstituted but could be discontinued after 30 min. Shortly thereafter, a second episode of cardiopulmonary decompensation occurred. Extracorporeal circulation was reinstituted for the 3rd time. Severe left ventricular failure became evident necessitating short-term manual cardiac massage. The pulmonary vascular resistance was 250 dynes/s per cm^{-5} at a pulmonary capillary wedge pressure of 15–20 mm Hg. No improvement of the patient's cardiac and pulmonary function was possible during reperfusion and weaning from cardiopulmonary bypass seemed impossible. It became evident that the patient would require temporary artificial cardiopulmonary support and the bypass circuit was exchanged for an extracorporeal membrane oxygenation system. Percutaneous vascular access was chosen using the right femoral vein and artery. The veno-arterial perfusion route was chosen since both cardiac and pulmonary support seemed necessary. Following transport to the intensive care unit, blood pressure and blood gases were stabilized by means of ECMO.

Several hours later progressive left ventricular failure occurred requiring the percutaneous insertion of an intra-aortic balloon pump (IABP) via the left femoral artery. Following additional IABP support, the patient could be stabilized. The next day, rethoracotomy was required for prolonged bleeding from the chest. The transplanted lung appeared oedematous and consolidated. On the 4th postoperative day, acute renal failure occurred requiring continuous arterio-venous haemofiltration (CAVHF) which was instituted between the inflow and outflow portions of the ECMO system. With the ECMO flow ranging between 2.6 to 3.3 l/min, arterial oxygenation was kept within the normal range. IABP support could be discontinued after 140 h. Attempts to wean the patient from ECMO on POD 3 and 5 were not successful as both cardiac and pulmonary failure developed rapidly on reduction of the extracorporeal blood flow (Figs. 1, 2). On day 8, a second re-exploration of the right chest was performed for severe bleeding which occurred after puncture of the subclavian vein. At that time, the lung appeared even more consolidated. In view of this finding combined with her persistently poor pulmonary function, retransplantation was scheduled.

After 232 h of ECMO perfusion, retransplantation of the right lung was performed. During the reoperation, a second venous inflow cannula was positioned in the right atrium to allow for increased extracorporeal blood flow. Retransplantation was successfully performed and the patient could be weaned from ECMO on the operating table.

CAVHF was continued until the 20th postoperative day, after which she underwent conventional dialysis over the next 2 weeks. The patient gradually recovered from the second operation and weaning from the respirator followed by extubation was accomplished on the 30th POD. However, due to cachexia and muscular weakness she could not sustain spontaneous breathing and was reintubated 3 days later. Over the next 10 days, 3 more unsuccessful attempts were made to wean her off the ventilator.

Considerable problems arose from the fact that she developed instability of both the main bronchus and the intermediate bronchus of the transplanted lung requiring implantation of an endotracheal stent on POD 55. This manoeuver improved her clin-

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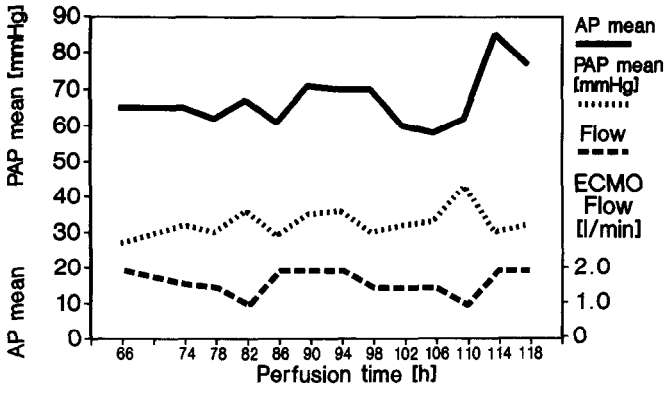

Fig. 1. Attempt to wean from ECMO: Haemodynamic response. This graph shows the time course of mean arterial blood pressure (AP mean), mean pulmonary pressure (PAP mean) and ECMO flows observed between the 3rd and 5th postoperative day in case 2. Weaning from ECMO was attempted on two occasions by stepwise reduction of the ECMO flow to 1 l/min. Weaning was not successful as demonstrated by the considerable increase of the PAP and corresponding decline of AP

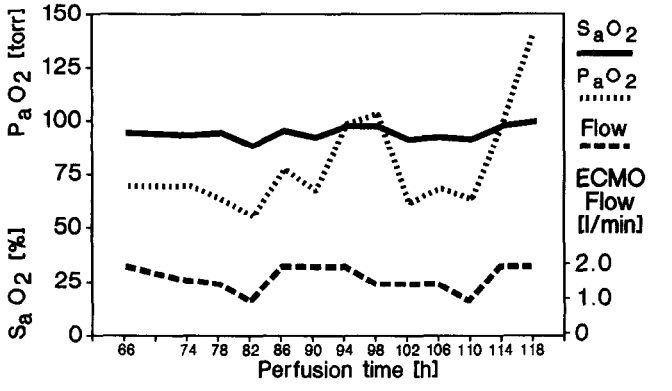

Fig. 2. Attempt to wean from ECMO: Pulmonary response. The time course of the arterial oxygenation saturation (SaO_2) and oxygen partial pressure (PaO_2) in blood samples drawn from the right radial artery are displayed together with the ECMO flows. The values were obtained between the 3rd and 5th postoperative day in case 2. Weaning from ECMO was attempted on two occasions by reducing the ECMO flow to 1 l/min. Weaning was not successful since PaO_2 dropped below 60 torr and SaO_2 fell below 90% each time the ECMO flow was reduced

ical condition significantly. With ongoing mobilization she was able to breathe spontaneously over considerable time periods every day and enjoyed the visits of her family. On the 110th POD interstitial (viral) and bacterial pneumonia developed and was followed by an episode of pulmonary rejection. She again became ventilator-dependent due to progressive pulmonary failure. Lung biopsies from the transplanted graft showed signs of chronic adult respiratory distress syndrome with interstitial fibrosis and interstitial pneumonia. The patient died on POD 159.

Discussion

At our institution, 17 single lung transplantations, 2 double lung transplantations and 15 combined heart-lung transplantations were performed between December 1987 and September 1990. In 3 patients, acute retransplantation of one lung was required. The only death in this series occurred in the patient described above. Extracorporeal circulatory support of the recipient during the initial implantation procedure became necessary in 7 of 17 single lung transplantations while both double lung transplantations were performed via a bilateral thoracotomy without the use of ECC. The main reason for institution of cardiopulmonary bypass during single lung transplantation was right heart failure due to high pulmonary vascular resistance after clamping of one pulmonary artery. In all but one instance, right atrial to femoral artery bypass was used.

Two of 3 patients in our series required prolonged ECMO support as a bridge to retransplantation of the lung. The use of ECMO has been commonly regarded as a relative contraindication to subsequent lung transplantation. One such case has been reported by the Toronto group [6] in 1984. Their patient underwent right lung transplantation for pulmonary failure from paraquat poisoning after having been supported by ECMO for 4 days before operation. Failure of the transplanted graft occurred and ECMO had to be reinstituted using a veno-venous perfusion route. After another 17 days of perfusion, the left lung was transplanted. ECMO support was discontinued 48 h after the second operation. The patient demonstrated considerable improvement of his clinical status but ultimately died from a tracheal defect which led to the development of a fistula between the innominate artery and trachea with sudden massive haemorrhage 2 months after the second operation. In a previous case reported by the Toronto group, ECMO was used for 4 days following right lung transplantation in order to support the recipient's cardiopulmonary function [5]. This patient died after weaning from ECMO on POD 18 because of disruption of both the pulmonary artery and right bronchial anastomoses.

At present, ECMO represents the only therapeutic option to support patients with pulmonary or combined cardiac and pulmonary failure. If ECMO is used for pulmonary support in the face of normal cardiac function, a veno-venous perfusion route clearly is preferrable. When returning the oxygenated blood to the venous system, hypoxaemia within the aortic arch does not occur which may complicate returning the blood into the femoral artery. This, in fact, has been a problem in both of the cases reported here. In the second case, arterial oxygen saturation was within normal limits (PaO_2 between 58 and 110 torr) in both the right radial and femoral artery provided that the entire "cardiac output" was supplied by the extracorporeal circuit. Problems occurred in both cases during retransplantation. The change from supine into a left decubitus position for thoracatomy considerably diminished the venous return to the oxygenator and extracorporeal blood flow declined significantly resulting in an inadequate arterial oxygenation in the upper half of the body. In both cases, placement of a second venous inflow cannula increased drainage of blood from the right atrium and flow rates of the pump associated with normalization of radial artery oxygen saturation.

This dividing of the circulation into a "blue" and a "pink" part when using the femoral artery for return of

the oxygenated blood is a known complication of veno-arterial ECMO in cases with preserved cardiac function. But despite these limitations in these 2 cases, veno-arterial perfusion routes were considered mandatory. In the first case, implantation of the ECMO system was necessary as an emergency procedure. It was anticipated that the patient would require only short-term ECMO support for retransplantation. Furthermore, it was our intention to continue ECMO throughout the operative procedure. Under these conditions, a veno-arterial bypass should be utilized to protect the right heart. In the second patient, both cardiac and pulmonary support was required. To achieve this goal only veno-arterial ECMO had to be used. A change of the perfusion route to veno-venous ECMO after reversal of left heart failure might have been an option which we did not choose in this case. Since the signs of cardiac failure observed in both cases may well be explained by perfusion of the coronary arteries by deoxygenated blood (in spite of satisfactory oxygen saturation in the radial artery), we would certainly prefer cannulation of the ascending aorta in future cases of veno-arterial ECMO in the setting of pulmonary transplantation. In view of this, the cerebral dysfunction which occurred in our first case might be attributed to temporarily decreased oxygen saturation in the cerebral blood flow.

In our experience, the use of percutaneous vascular access for institution of ECMO support has greatly reduced bleeding complications from the insertion site. We have employed percutaneous vascular access in our 12 most recent cases to install both veno-venous and veno-arterial ECMO without the use of a fluoroscope and without any vascular complications.

There are three main reasons for development of early graft failure after lung or combined heart-lung transplantation. Insufficient protection of the graft against ischaemic damage can result in pulmonary failure. The "reperfusion response" of a previously ischaemic lung with pulmonary oedema, decreased arterial blood oxygenation and increased pulmonary vascular resistance may occur within the first 24 h after transplantation. Complications unrelated to ischaemia such as pneumonia or allograft rejection may result in pulmonary failure after transplantation.

Both entities were responsible for the development of early graft failure in our patients. In the first case, early signs of pneumonia starting in the lower lobe of the graft were detected but remained refractory to vigorous drug treatment. Since the pneumonia occurred immediately postoperatively, it might be suspected that this pneumonic infiltrate was pre-existing in the donor and was not recognized prior to retrieval of the graft. In the second case, both cardiac and pulmonary failure developed. Upon reperfusion, the lung graft appeared slightly oedematous but was well perfused and ventilated initially, providing adequate arterial oxygenation. With ongoing reperfusion, however, the pulmonary vascular resistance rose significantly resulting in right ventricular failure. Her lung exhibited large areas of atelectasis within the lower lobe refractory to positive pressure ventilation. Whether these phenomena can be attributed to insufficient protection of the graft or represent symptoms of an early reperfusion response remains speculative but cannot completely be disregarded. No such symptoms were noted in our previous experience. Our method of pulmonary preservation has been developed and tested experimentally in our laboratories [2]. We utilize pulmonary flush perfusion with modified Euro-Collins solution and pre-infusion of a prostacyclin analogue. This method of lung preservation provided adequate post-ischaemic pulmonary function in all patients after lung or combined heart-lung transplantation.

These two cases demonstrate that ECMO is feasible for successful bridging to retransplantation of the lung even under the adverse conditions of continued immunosuppression and emergency retransplantation. The use of ECMO for temporary support of the recipient's pulmonary function does not represent a contraindication to subsequent lung transplantation.

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Discussion

Dr. D. Loisance (*Creteil, France*). I thank you for the opportunity to discuss this paper. These two cases illustrate clearly how far we can get, that we should not go too far with all these improvements in modern technology, and they show the enormous progress made in the field of extracorporeal oxygenation and perfusion.

I am wondering about some technical details. First of all, have you given special attention to platelet function preservation and to the coagulation system? I would appreciate your comments on the pharmacological pretreatment of your patients. The second question is related to the strategy itself. I don't understand why in the first case you preferred a retransplantation of the failing lung to a transplantation of the controlateral lung. In the second case, why did you select ECMO support to retransplantation instead of ECMO bridge to heart and lung transplantation.

Mr. R. Millner (*London, UK*). In a case of heart-lung transplantation that *Dr. Yacoub* was involved in, we actually used veno-venous ECMO rather than veno-arterial ECMO, as was done here. I would be interested to hear the comments of the presenter as to why they didn't use veno-venous ECMO, which I think is probably a safer procedure.

Dr. M. J. Jurmann (*Hannover, FRG*). I'd like to thank *Dr. Loisance* and *Mr. Millner* for their comments. To start out with the last question: we did not use veno-venous ECMO in the first case, as it was anticipated that the patient would require only short-term ECMO support. She was awaiting acute retransplantation, and it was forseeable that this was going to be performed within the next few hours. Also, it was clear that she would require continuation of ECMO support during her second operation. In the setting of lung transplantation, the intra-operative use of a veno-arterial bypass is clearly advantageous compared to veno-venous perfusion with regard to the achievement of protection of the right heart during the implantation procedure. So, for these reasons use of veno-arterial ECMO seemed preferable in her case. Probably more important is the question of why we have not chosen a veno-venous ECMO in our second case. In this patient, we were faced with a combination of both substantial cardiac and pulmonary failure. Therefore, she required artificial support of both heart and lungs and the only system which can provide such is a veno-arterial ECMO circuit. It was obvious that there was no other choice than to institute a veno-arterial ECMO system in her case.

We are aware of the limitations of long-term veno-arterial ECMO support in cases of pulmonary failure. It is now well recognized that if one uses a short cannula for femoral return of the oxygenated blood to the patient, problems are likely to occur with respect to hypoxemic blood flowing through the aortic arch. Use of a veno-venous perfusion route for ECMO can prevent the occurrence of this phenomenon and is clearly preferable in cases of severe pulmonary failure. Regarding the course of our patients, the development of both severe neurologic damage in the first case and myocardial failure present in the second case might be attributed to temporary hypoxaemia within the cerebral and coronary vascular bed. The temporary nature of both phenomena most likely supports this hypothesis.

With regard to comments from *Dr. Yacoub's* group about previous experience using ECMO as a bridge device to lung transplantation, I need to remind you of two patients who were reported from the early experience of the Toronto group. Most of you are aware of these two cases. In one, they bridged to a lung transplantation; in another case bridging to retransplantation of the lung was performed. Unfortunately, both patients died.

With respect to *Dr. Loisance's* question about our anticoagulation protocol for ECMO, we did not take any special precautions. In these patients a continuous heparin drip is used to adjust the ACT to between 150 to 250 s. We are aware of the fact that preservation of platelets can be achieved by the use of drugs like aspirin, dipyramidol of certain prostaglandins. Also, aprotinin might be incorporated in such a proctocol. We appreciate this comment for further consideration.

The next question by *Dr. Loisance* was why we have not opted for subsequent transplantation of the contralateral lung in the first case. The reason was that this patient had a fixed diaphragm, progressive shrinking of the contralateral lung and a considerably reduced intrathoracic volume in the contralateral chest secondary to fibrosis, so single lung transplantation on the right side was the obvious treatment choice for her. We would have had substantial problems or it would have been almost impossible to transplant her left lung. Regarding our second case, I found your comment very interesting about why we did not use subsequent combined heart-lung transplantation to solve the problems of this patient. Our main consideration against such a procedure was that we believed her myocardial failure to be of a temporary nature. We assumed that the myocardial failure present had its origin in temporary myocardial hypoxaemia and elevated pulmonary vascular resistance during reperfusion of the transplanted lung. It therefore was estimated to represent a reversible phenomenon. In the end, we were right about this point, but your suggestion certainly would have been an option had cardiac failure persisted.